

Art Unit: 1654

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I (claims 1-7) and election of anti-human IgG antibody form the goat in the reply filed on 3/17/09 is acknowledged. The traversal arguments were answered in the office action dated 4/2/09.

Status of pending claims

Applicant's amendment to claims in the response filed on 9/2/09 has been acknowledged.

Claims 1-11 are pending.

Claims 9, 10 and 11 have been as new claims.

Claim 8 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in the reply filed on 3/6/09.

Claims 1-7 and 9-11 are examined on the merit.

Any objections and/or rejections made in the office action dated 4/2/09 and not specifically discussed below in its original or modified form here are considered withdrawn.

Maintained Rejections

Claim Objection

Claims 7 and 11 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. In this particular instant

Art Unit: 1654

claim 7 does not further limit the base claim 1 and claim 11 does not limit the claim 10 from it depend from. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 recites that optionally feeding the reaction mixture into the delay structure and does not recite that a micromixer is present in the delay structure to re-circulate. However, claim 7 recite that the reaction mixture is pumped in circulation and a micromixer is optionally used. In a similar way claim 10 recites that the reaction mixture is retained in the delay structure for pre-determined time and does not recite re-circulating the reaction mixture or using a micromixer. However, claim 11 recite that the reaction mixture is pumped in circulation and a micromixer is inserted into the structure.

Please note: The earlier rejection of claim 7 under 35 USC 112, 2nd paragraph has been modified to a claim objection. However, the earlier rejection and the instant objection are based on “further limiting the subject matter of a previous claim”.

Response to Arguments

Applicants argue that “[C]laim 1 requires feeding to a micromixer, mixing intensively in the micromixer and then optionally feeding from the micromixer into a delay structure. Claim 1 is silent about the structure of the delay structure. Claim 7 provides details on the delay structure, providing that the reaction mixture is pumped in circulation in the delay structure, and further that a micromixer is optionally inserted into the circuit. Thus, claim 7 is properly dependent on claim 1. Claim 1 mentions feeding to the micromixer and then optionally feeding to a delay

Art Unit: 1654

structure. Claim 7 incorporates these same requirements, and then further provides that the delay structure itself optionally contains a micromixer. The micromixer in the delay structure would be in addition to the micromixer mentioned in claim 1. In other words, claim 7 contemplates the possibility of using two micromixers -- one outside the delay structure (the micromixer mentioned in claim 1) and one inside the delay structure (the optional micromixer mentioned in claim 7). Respectfully, claim 7 is clear and is properly dependent on claim 1. An early notice to that effect is earnestly solicited”.

Applicant's arguments filed 9/2/09 have been fully considered but they are not persuasive. By stating that “claim 1 is silent about the structure of the delay structure” applicants acknowledge that instant claim 1 is only defining the delay structure as an option. It does not define the delay structure. Hence the claim 7 that depends from the claim 1 defines the delay structure with optional addition of micromixer. In claim 1 the second micromixer is not optional and there is no mention of second micromixer. As acknowledged by the applicants “Claim 1 mentions feeding to the micromixer and then optionally feeding to a delay structure.” There is no mention of a second micromixer in the delay structure. Like wise the new claim 11 requires that recirculation of reaction mixture in the delay structure using a second micromixer inserted in the delay structure. However, claim 10 requires “retaining the reaction mixture in the delay structure for a predetermined time by the volume of the delay structure and the flow rate of the reaction mixture into the delay structure. There is no mention of second micromixer being present in the delay structure. Hence claims 7 and 11 does not further limit the limitations recited in the base claims 1 and 10 from which they depend from.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 9 and 10 remain rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Spikmans, 2002, Rapid Communications in Mass Spectrometry, 16, 1377-1388. the rejection has been modified to accommodate amendments filed on 9/2/09. Response to applicant's response appears at the end of the reiterated, modified rejection.

Art Unit: 1654

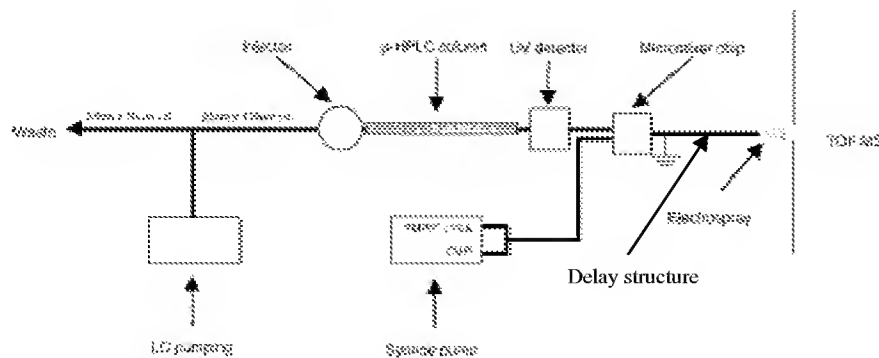
In the instant application, applicants claim a process for labeling biomolecules by reacting the reactive functional groups of biomolecules with a label. The process comprises, i) feeding solutions of both compounds in defined quantitative rates to a micromixer and ii) mixing intensively there. The process steps also comprises optional steps such as iii) feeding the reaction mixture into a delay structure, iv) retaining the (reaction mixture) there (in the delay structure) for a time predetermined by volume of the delay structure and flow rate of reaction mixture and v) terminating the reaction after a time predefined by the reaction condition.

Although, office has assigned Roman numerals to the different process steps, it is not required that the steps be performed in the same order as numbered or in any particular order, because the instant claim is drawn with the transitional phrase “comprising”. The Roman numerals have been assigned by the office to help organize and craft the rejection properly.

As recited the invention claims a process of labeling biomolecules that bears free reactive groups with a label compound and forms a covalent bond. As presented the process requires feeding solutions of both compounds in defined quantitative flow rates to a micromixer and mixing intensively there. The other steps are being optional as recited.

Spikmans discloses a method of labeling amines, ketones and aldehydes (reads on instant claim 2) with a positively charged phosphonium compound for preionization of the analytes (page 1378, column 2, paragraph 2). As shown in figure 1 on page 1379 (reproduced as shown below), the sample (the compound of the instant invention) after undergoing separation by HPLC enters the micromixer chip (micromixer of the instant invention) via a UV detector.

Art Unit: 1654



The reagents for the derivatization (for labeling) are introduced into the second inlet of the micromixer chip by a dual syringe pump (page 1380, column 2, paragraph 1). Spikmans further discloses that all parameters of the reaction such as flow rates and concentrations can be defined separately for optimization of the reaction and thus help or promote product formation (page 1380, column 2, paragraph 2). This reads on the steps (i) of the instant claim 1. Spikmans also discloses that microchip layouts have been proposed for mixing, including turbulent mixing and serial and parallel lamination (page 1378, column 1, paragraph 3). Since the reaction occurs in ‘seconds’ compared to 30 minutes reaction ‘on the bench’, it inherently implies that the reagents introduced into the micromixer mixes intensively to form products and hence reads on the step (ii) of instant claim 1. Spikmans also discloses that the method of labeling can be used for labeling n-terminus of a peptide (page 1381, column 1) and this reads on the biomolecule of instant claim 1. The fact that Spikmans discloses the labeling N-terminus of a peptide reads on the instant claim 10. The instant claim 1 is drawn to a process for labeling biomolecules, an intended use. The process of Spikmans includes in-line optical detectors including UV and fluorescence (abstract). Spikmans further discloses that “when fluorescence detection is preferred, a fluorescence tag can be built into the reagent instead of positive phosphonium group

Art Unit: 1654

(page 388, column 1, paragraph 4). This reads on instant claims 9 and 10 where a dye is used as the label.

Spikmans also discloses that in a study to emulate on-chip band broadening, the total volume of the system (micromixer) with the chip was mimicked in a system without the chip using a 100- μm inner diameter capillary. This inherently implies that the channel in the micromixer has diameter $\sim 100\ \mu\text{m}$. This reads on the instant claim 4.

Spikmans also discloses that the micromixer that is developed is based on parallel lamination (page 1378, column 2, paragraph 1). This reads on the instant claim 5.

The figure 3 of the Spikmans discloses a connecting structure, i.e., a tube or capillary tube (as pointed out by an arrow in the figure above) that connects the micromixer to the mass spectrometer. This connecting capillary tube corresponds to the delay structure of the instantly claimed process. This connecting structure is of predefined volume determined by its defined length and cross sectional diameter of the tubing. This reads on the instant claim 6.

The reference of Spikmans does not explicitly teach that their process is used for the labeling of proteins, nucleic acids and/or saccharides.

However, Spikmans discloses that the method of labeling small molecule amines can be used for labeling N-terminus of a peptide (page 1381, column 1) and this reads on the biomolecule of instant claim 1 and the polypeptide (protein) of claim 6. Where applicant claims a process of labeling a protein or an antibody (elected species) a characteristic not explicitly disclosed by the reference, a 102/103 rejection is proper according to MPEP 2112. MPEP 2112 states that “[W]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function

Art Unit: 1654

is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims".

Response to Arguments

1. Applicants argue that office considers the preamble "a process for labeling biomolecules" as an intended use. Applicants argue that the body of the claim makes reference back to the preamble and used the preamble to define their invention and office must give weight to the preamble and not ignore it. Applicants further state that Spikmans discloses a method for labeling amines, ketones and aldehydes and the office has not made a that these are biomolecules and that these biomolecules are labeled according to Spikmans' process.

Applicant's arguments filed 9/2/09 have been fully considered but they are not persuasive. Although in the office action mailed 4/2/09 office indicated that the process for labeling biomolecule as an intended use, it should be noted the office action points out that the method of labeling can be used for labeling N-terminus of the peptide (page 12) that has reference to page 1381, column 1 of Spikmans. Moreover, a process that is meant for labeling amines, aldehydes and ketones clearly implies that the method can be used for labeling

Art Unit: 1654

molecules that exhibits these functional groups and biomolecules exhibits such functional groups.

2. Applicants argue that the European application has been granted and applicants respectfully submit that the Spikmans process has clearly described limitations that would make it unsuitable for use in labeling biomolecules on a large scale and hence persons skilled in the art would not have been motivated to adapt Spickmans's process.

Applicant's arguments filed 9/2/09 have been fully considered but they are not persuasive. Approval of the application in European patent office has no bearing on the prosecution of the application under US patent laws. With regards to applicant's remarks that Spikmans's process has clearly described limitations that would make it unsuitable for labeling biomolecules on a large scale, applicants have not pointed out any such limitations supporting their arguments.

3. Applicants argue that the process of Spikmans accounts for a maximum yield that is below 50% and the instant invention as presented in paragraphs [0063] and [0070] of published application shows improved sample quality and improved sample activity. These advantages of the inventive process are neither disclosed nor suggested by Spikmans.

Applicant's arguments filed 9/2/09 have been fully considered but they are not persuasive. It should be noted Spikmans clearly states that "[T]he reaction conditions were chosen such that only a maximum of 50% of the benzylamine could react with the TMPP+ to

Art Unit: 1654

form the pre-ionized product" (page 1383, paragraph 1). Spikmans also suggest that an optimum compromise between flow rate and yield needs to be determined (page 1384, column 1, paragraph 1). Spikmans further states that "all parameters for the reaction such as flow rates and concentrations can be defined separately for optimization of the reaction and thus product formation" (page 1380, column 2, paragraph 2). Moreover, the statement regarding the improved activity that the applicants have claimed by pointing out to section [0070] clearly states that "the sample prepared by the micromixer exhibited **slightly** improved activity in the subsequent activity test compared to the conventionally prepared sample" (emphasis added by the office).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). Applicant's amendment to the claims does not overcome the rejection on record as illustrated above.

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Art Unit: 1654

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
Primary Examiner, Art Unit 1654